REMARKS

Applicant has incorporated the limitation of claim 12 into independent claim 11, which now recites a DNA encoding a substantially detoxified mutant of at least a portion of the sequence of the S1 subunit of *B. pertussis* toxin. The mutant comprises an epitope that contributes to immunoprotection against *B. pertussis* toxicity. The DNA encodes a mutation wherein arginine 9 is replaced with another amino acid. Applicant has canceled claims 12 and 14, and changed the dependencies of claims 13 and 15.

Applicant also has canceled claims 17-22, without prejudice or disclaimer. These claims were withdrawn from consideration because they recite the *B. pertussis* mutant. Applicant reserves the right to prosecute the subject matter of any canceled claim in one or more divisional and/or continuation application(s).

Claim 11 and dependent claims 13 and 15-16 are thus believed clearly allowable.

RENEWED REQUEST FOR INTERFERENCE

On October 5, 1992, in accordance with the provisions of 37 CFR §§1.604 and 1.607, applicant requested an interference between this application and the following patent and applications:

1. U.S. Patent No. 5,085,862 to Klein *et al.* **("Klein '862")** and any pending continuing applications claiming related subject matter;

2. Application Serial No. 07/094,307 filed September 4, 1987 ("the '307 application");

3. Application Serial No. 07/232,482 filed August 17, 1988 ("the '482 application"); and

4. Application Serial No. 07/632,265 filed December 21, 1990 ("the '265 application").

Applicant proposed the following count directed to a mutant protein for the interference:

Proposed Count 1(A)

> A substantially detoxified mutant of at least a portion of the S1 subunit of *Bordetella pertussis* toxin, said mutant comprising an epitope that contributes to immunoprotection against *Bordetella pertussis* toxicity.

Alternatively, applicant proposed the following count because the involved patent and applications also disclose the DNA encoding such proteins:

Proposed Count 1(B)

> A DNA molecule encoding a substantially detoxified mutant of at least a portion of the S1 subunit of *Bordetella pertussis* toxin, said mutant comprising an epitope that contributes to immunoprotection against *Bordetella pertussis* toxicity.

Applicant no longer believes that an interference between the subject application and Klein '862 would be proper. The subject application claims DNA molecules, whereas Klein '862 claims protein molecules. Rather, applicant believes that the subject matter of any interference involving this application should be limited solely to a DNA encoding a *B. pertussis* toxin mutant having an amino acid substitution at the 9 position, as claimed above. Accordingly, only applications or patents which claim DNA encoding such a mutant at position 9 should be involved in any interference.

Therefore, applicant proposes that the following count be used for the interference:

Proposed Count 1

> A DNA molecule encoding a substantially detoxified mutant of at least a portion of the sequence of the S1 subunit of *Bordetella pertussis* toxin, said mutant comprising an epitope that contributes to immunoprotection against *Bordetella pertussis* toxicity, wherein said DNA encodes a mutation wherein arginine 9 is replaced with another amino acid.

Clearly, DNA encoding such a mutant is novel, unobvious and separately patentable over DNA encoding other specific or generic *B. pertussis* toxin mutants. Indeed, the substitution at arginine 9 has been recognized in the art as resulting in a superior S1 analogue. Burnette *et al.*, *Science* 242: 72-74 (1988) (APPENDIX 1), have disclosed the production of 13 different S1 mutants using site-directed mutagenesis. *See* Table I at page 73. Among the five, single site-directed analogues, the Arg^9-Lys analogue alone had reduced enzymatic activity and unlike the double mutants, maintained reactivity with a neutralizing mAb. For instance, ADP-ribosyltransferase activity was reduced by a factor of **approximately 5000**; glycohydrolase activity was reduced by a magnitude of 50 to 100. When the Arg9 mutation was introduced into a full length recombinant S1, Burnette *et al.* found that transferase activity was reduced by a factor of **approximately 1000**. Burnette *et al.* conclude that "[t]his observation indicates that the substitution at residue 9 is alone sufficient to attain the striking loss in enzyme activity. . ." Page 74, column 1, middle paragraph.

Similarly, Pizza *et al.*, *SCIENCE*, 246: 497-500 (1988) (APPENDIX 2) disclose the site-directed mutagenesis of the S1 subunit. In the R9K mutation, Arg^9 was substituted

with Lysine. Introduction of this mutation into the holotoxin resulted in a superior reduction of toxicity in CHO cells and in ADP-ribosyltransferase activity when compared with other mutations, R13L (Arg13 to Leu) and E129G (Glu 129-Gly). *See* Table 1, page 498. This substitution did not impair binding with protective monoclonal antibodies.

If there are no other applications or patents claiming DNA encoding the 9 position mutant, applicant respectfully requests that the claims be allowed and forwarded to issue.

Applicant concurrently petitions for a one month extension of time to enable this paper to be considered. The Commissioner is authorized to debit the undersigned's Deposit Account No. 19-0741 for the extension fee and any underpayment or credit any overpayment. If additional extension(s) of time are required, applicant expressly petitions for such extension(s) and the Commissioner is authorized to debit the undersigned's Deposit Account No. 19-0741 for the requisite fee.

The Examiner is courteously invited to contact the undersigned should the Examiner have any questions which might be resolved over the telephone.

Respectfully submitted,

March 8, 1994
Date

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